Organocatalytic enantioselective functionalization of indoles in the carbocyclic ring with cyclic imines†

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An organocatalytic enantioselective functionalization in the carbocyclic ring of indoles with benzoxathiazine 2,2-dioxides is described using a quinine-derived bifunctional organocatalyst. This aza-Friedel–Crafts reaction provides 4-indolyl, 5-indolyl and 7-indolyl sulfamidate derivatives in good yields (up to 99%) and with moderate to high enantioselectivities (up to 86% ee).

Introduction

The catalytic asymmetric Friedel–Crafts reaction[1] of aromatic compounds with imines is one of the most important methodologies for the synthesis of enantiopure chiral benzylic amines, which are present in a wide range of pharmaceutical and natural products.[2] In this context, the enantioselective addition of indoles to imines is one of the most studied asymmetric Friedel–Crafts reactions,[3,4] due to the importance of the indole scaffold in natural product synthesis, medicinal and agrochemical industries and materials science.[5] However, the majority of methods on the enantioselective aza-Friedel–Crafts reaction of indoles involve the functionalization of the C-3 position.[4] Additionally, different examples of the asymmetric functionalization at the C-2 position of indoles with imines have been described.[6] In contrast, the enantioselective functionalization in the carbocyclic ring of indoles is hardly studied in the literature and represents a great challenge in asymmetric catalysis (Fig. 1A).[7] We have recently presented a methodology for the organocatalytic enantioselective functionalization of the carbocyclic ring of indoles using as an activating/directing group, a hydroxy group.[8–10] Hydroxyindoles, in the presence of bifunctional organocatalysts, react as phenols, even when the positions in the azole ring remained unsubstituted. Given the remarkable significance of chiral indoles bearing a nitrogen in the a-position and hydroxyindoles (Fig. 1B), the development

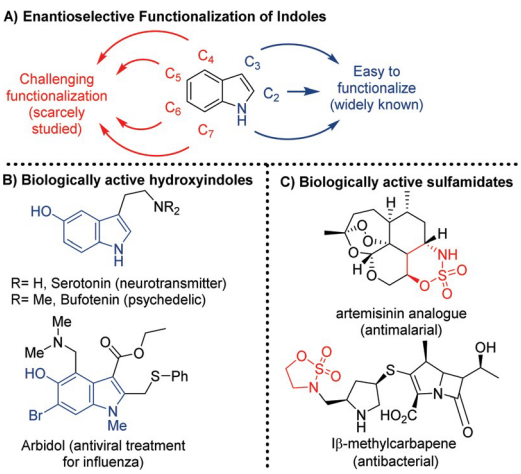

Fig. 1 Enantioselective functionalization of indoles. Examples of biologically active hydroxyindoles and sulfamidates.

of new methodologies for the synthesis of chiral indolyl amines is the great interest for organic synthesis.

In this communication, to accomplish the enantioselective functionalization in the carbocyclic ring of indoles, we have chosen cyclic imines (benzoxathiazine 2,2-dioxides) as electrophiles. Very recently, benzoxathiazine 2,2-dioxides have attracted attention in asymmetric catalysis, because these compounds have been proved to be powerful building blocks for the synthesis of chiral benzosulfamidate heterocycles. In this context, several sulfamidates have shown important biological activities[11] (Fig. 1C) and several examples of enantioselective reactions have been described using these cyclic imines as electrophiles.[12] However, the number of enantioselective aza-Friedel–Crafts reactions using benzoxathiazine 2,2-dioxides is scarce.[13,14] In 2017, Kim has described the organocatalytic enantioselective alkylation of

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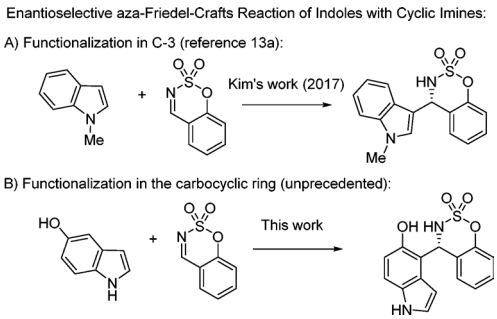


Scheme 1 Enantioselective aza-Friedel–Crafts reaction of indoles with cyclic imines.

indoles at the C-3 position with cyclic imines catalyzed by chiral Brønsted phosphoric acid (Scheme 1A).[13a] The corresponding 3-indolyl sulfamidate derivatives were obtained with excellent yields and enantioselectivities. Herein, we described a complementary methodology for obtaining chiral indolyl sulfamidates (Scheme 1B). By using a quinine-derived bifunctional organocatalyst, we achieve the functionalization of the carbocyclic ring of hydroxyindoles with cyclic imines, obtaining 4-indolyl, 5-indolyl and 7-indolyl sulfamidate derivatives (Scheme 1B).

Results and discussion

We chose the aza-Friedel–Crafts reaction between benzoxathiazine 2,2-dioxides (1a) and 4-hydroxyindole (2) for the optimization studies. Different bifunctional organocatalysts derived from *Cinchona* alkaloids (Fig. 2) in CH_2Cl_2 at room temperature were screened (Table 1). When quinine (I) was tried as a catalyst, the regioselectivity was poor and we observed 3 compounds after 21 h of reaction (Table 1, entry 1). The major product was the corresponding hydroxyindole alkylated at the C-5 position (3a) in 48% yield but was a racemic mixture. Then, we isolated as an inseparable mixture after column chromatography, the product alkylated at the C-7 position (4a) and the double alkylated product at C-5 and C-7 positions (5a, a mixture of diastereoisomers in 1 : 1 ratio determined by ^{1}H NMR). Different bifunctional organocatalysts such cupreines, thioureas and squaramides were tested,[15] but we found that 9-*O*-benzylcupreine (II), derived from quinine, was the only one with a promising enantioselectivity (33% ee, entry 2). However, product 5a was still

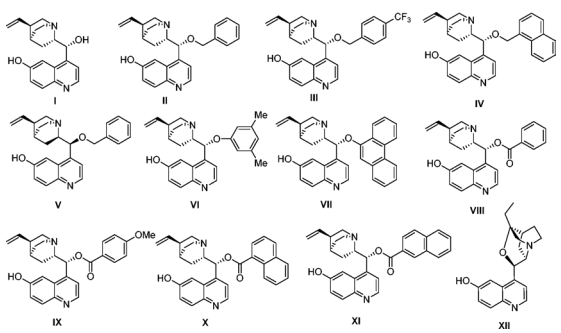
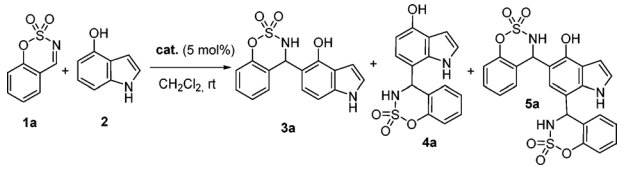


Fig. 2 Bifunctional organocatalysts screened.

Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst (5 mol%)	*t* (h)	3a yield[b] (%)	3a ee[c] (%)	4a yield[d] (%)	5a yield[d,e] (%)
1	I	21	48	0	6	34
2	II	24	57	33	9	28
3	III	5	56	31	8	23
4	IV	16	39	33	10	36
5	V	6	42	−8	8	30
6	VI	6	60	35	11	26
7	VII	6	58	42	10	21
8	VIII	24	39	33	10	36
9	IX	24	47	41	14	29
10	X	16	49	36	8	22
11	XI	6	48	43	15	24
12	XII	6	45	13	9	32

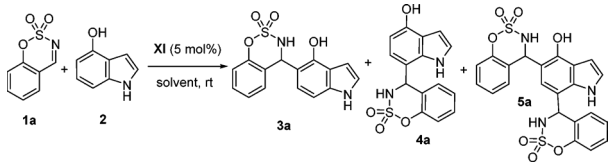
[a] Reaction conditions: 1a (0.1 mmol), 2a (0.2 mmol) and catalyst (5 mol%) in 1 mL of CH_2Cl_2 at room temperature. [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC. [d] Determined by ^{1}H NMR. [e] The dr of compound 5a was around 1 : 1 in all cases, determined by ^{1}H NMR.

obtained with high quantity (28%). We tried several cupreine derivatives with a variety of substituents on the secondary hydroxyl group. The best catalyst in terms of enantioselectivity was catalyst XI, giving compound 3a in 48% yield, and 43% ee in 6 h (entry 11).

Next, we examined different solvents (Table 2), obtaining the best enantioselectivities with chlorinated solvents. In particular, when the reaction was run in 1,2-dichloroethane, compound 3a was obtained with 57% ee (entry 3, Table 2). Then, the effect of the reaction temperature was investigated. By lowering the reaction temperature to 4 or −20 °C, or increasing to 50 °C, the enantioselectivity was worse than that at room temperature. Afterward, different concentrations (entry 13 and 14) were tested without any improvement in the enantiomeric excess. Finally, different catalyst loadings were evaluated (entries 15–17), obtaining an enhancement of the enantiomeric excess to 67% ee and 46% yield, when 2 mol% of catalyst was used (entry 16). Our efforts to improve the enantiomeric excess of compound 3a were unsuccessful; therefore, we decided to study the scope and generality of the reaction under the conditions shown in entry 16, Table 2.

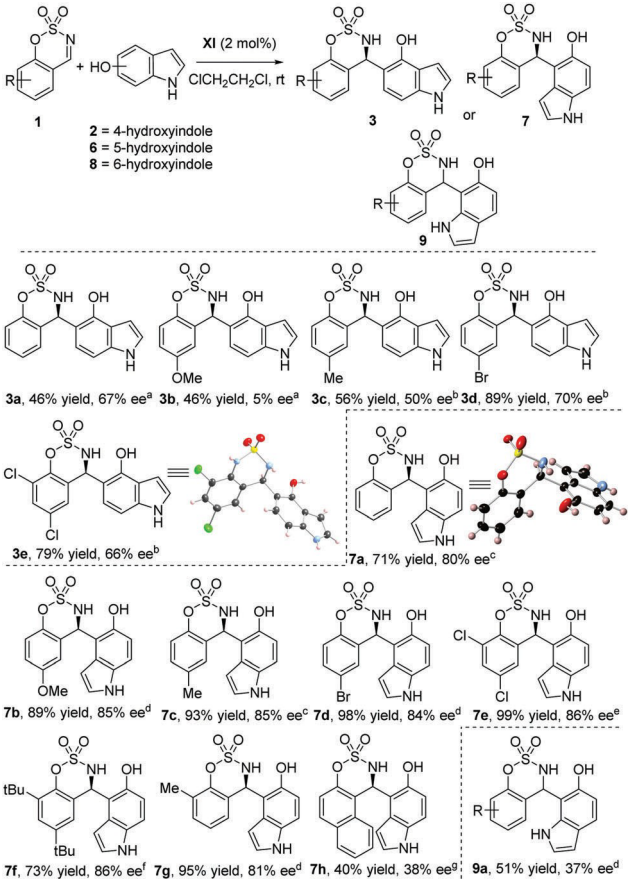
First we studied the effect of the substituents in the cyclic imines using 4-hydroxyindole as a nucleophile (Scheme 2). The presence of a strong electron-donating group (MeO) at the 6 position led to a nearly racemic mixture, while the presence of electron-withdrawing groups at the 6 position (Br) led to an improvement of the yield of product 3d to 89%[16] maintaining the enantioselectivity (70% ee). Once that we studied the reaction with 4-hydroxyindole, we decided to apply our methodology for the functionalization of indoles in every position of the carbocyclic ring. So, we continued our research studying the reaction of 5-hydroxyindole (6) and differently substituted benzoxathiazine

Table 2 Optimization of the reaction conditions[a]



Entry	Solvent	T (lC)	t (h)	3a yield[b] (%)	3a ee[c] (%)	4a yield[d] (%)	5a yield[d,e] (%)
1	CH_2Cl_2	20	6	48	43	15	24
2	$CHCl_3$	20	5	36	41	n.d.	n.d.
3	$ClCH_2CH_2Cl$	20	5	53	57	13	22
4	Toluene	20	18	29	17	18	23
5	Et_2O	20	18	52	8	12	10
6	THF	20	24	24	10	8	5
7	EtOAc	20	24	41	11	12	8
8	CH_3CN	20	24	27	32	8	10
9	MeOH	20	24	25	22	22	17
10	$ClCH_2CH_2Cl$	−20	24	43	49	17	28
11	$ClCH_2CH_2Cl$	4	5	53	54	13	20
12	$ClCH_2CH_2Cl$	50	6	57	45	14	19
13[f]	$ClCH_2CH_2Cl$	20	2	50	43	16	22
14[g]	$ClCH_2CH_2Cl$	20	6	61	35	15	13
15[h]	$ClCH_2CH_2Cl$	20	4	53	53	15	27
16[i]	$ClCH_2CH_2Cl$	20	6	46	67	14	22
17[j]	$ClCH_2CH_2Cl$	20	6	56	41	20	23

[a] Reaction conditions: 1a (0.1 mmol), 2a (0.2 mmol) and XI (5 mol%) in 1 mL of solvent. [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC. [d] Determined by ^{1}H NMR. [e] The dr of compound 5a was around 1 : 1 in all cases by ^{1}H NMR. [f] The reaction was performed in 0.35 mL of solvent. [g] The reaction was performed in 3 mL of solvent. [h] 10 mol% of catalyst was used. [i] 2 mol% of catalyst was used. [j] 0.5 mol% of catalyst was used.

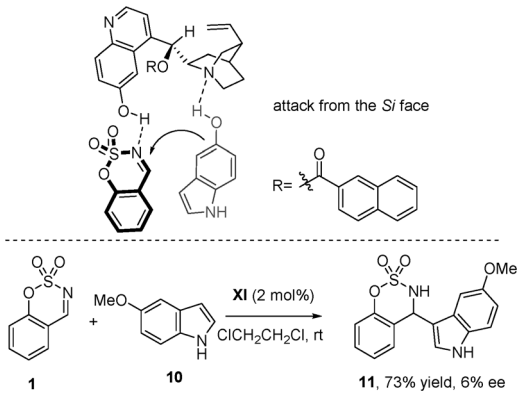


Scheme 2 Scope of the enantioselective aza-Friedel–Crafts reaction of hydroxyindoles with cyclic imines. Reaction conditions: 1 (0.1 mmol), hydroxyindole (0.2 mmol) and XI (2 mol%) in 1 mL of $ClCH_2CH_2Cl$. Isolated yields after column chromatography. Determined by chiral HPLC. [a] 6 h reaction time. [b] 15 h reaction time. [c] 48 h reaction time. [d] 72 h reaction time. [e] 3 h reaction time. [f] 144 h reaction time. [g] 240 h reaction time.

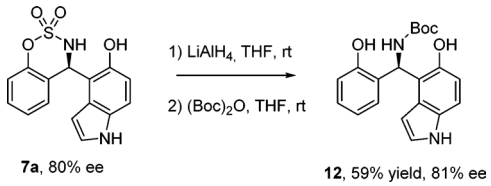
2,2-dioxides. To our delight, the corresponding product 7a, regioselectively alkylated at the 4 position, was obtained with good yield (71%)[17] and good enantiomeric excess (80% ee). The introduction of substituents in the aromatic ring of the cyclic imines revealed that both electron-donating and -withdrawing groups were well-tolerated at the 6 position on the ring (7b–7d, 89–98% yield and 84–85% ee). Moreover, cyclic imines (1e–1f) with two substituents that provide steric hindrance were suitable substrates for the aza-Friedel–Crafts reaction, affording good enantiomeric excess (86% ee) and good yields (99% and 73%). In addition, benzoxathiazine 2,2-dioxides bearing functional groups in the 8-position were also tolerated as substrates giving the reaction product 7g, with good yield (95%) and enantiomeric excess (81%). However, a naphthyl ring was not tolerated and the corresponding product was obtained with a moderate yield and enantioselectivity.[18] Unfortunately, 6-hydroxyindole showed low reactivity under the optimized reaction conditions, the 7-alkylated product 9a was obtained with complete regioselectivity, but a moderate yield (51%) and low enantioselectivity (37% ee) after 3 days of reaction. Finally, 7-hydroxyindole was also tested under the optimized reaction conditions, but unfortunately the regioselectivity was low obtaining a ratio of 1 : 1 of alkylated products at C-6 and at C-4, and the enantiomeric excesses of these compounds were also very poor.[15] We attribute these results to the interference between the NH of the indole group and the hydroxyl group.

The absolute configuration of compounds 3e and 7a was determined to be (*R*) by X-ray analysis[19] (Scheme 2), and for the rest of the products 3 and 7 was assigned on the assumption of a uniform mechanistic pathway. The observed stereochemistry can be explained through a plausible transition state depicted in Scheme 3, where the catalyst activates both the nucleophile and the electrophile through hydrogen bonding. The hydrogen bonding between the quinuclidine tertiary amine and the hydroxyl group of indole can be ascertained due to the different reactivities of 5-methoxyindole (10). When 10 was used as a nucleophile under the optimized reaction conditions, the reaction took place at the C-3 position of the indole (the normal position for a Friedel–Crafts alkylation) and the corresponding product 11 was obtained with good yield (73%), but nearly racemic (6% ee).

Finally, we carried out the reduction of the sulfamidate moiety[20] of compound 7a (Scheme 4), using $LiAlH_4$ obtaining the corresponding chiral amine bearing phenol and hydroxyindole moieties, which was protected *in situ* as its Boc derivative 12, with good yield (59%) and preserving the enantiomeric excess of compound 7a (81% ee).



Scheme 3 Elucidation of the bifunctional mode of activation.



Scheme 4 Synthetic transformation.

Conclusions

In summary, we have described an enantioselective functionalization in the carbocyclic ring of indoles through an aza-Friedel–Crafts alkylation reaction of hydroxyindoles with benzoxathiazine 2,2-dioxides as electrophiles using a quinine-derived bifunctional organocatalyst. The corresponding chiral sulfamidates were obtained with good yields and from moderate to good enantioselectivities. In general, the best yields and enantioselectivities were obtained when 5-hydroxyindole was used as a nucleophile, the reaction occurring at the C-4 position of the carbocyclic ring. This methodology represents the first Friedel–Crafts alkylation in the carbocyclic ring of indoles with cyclic imines.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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15 See the ESI† for further details.

16 We did not observe the formation of the 7-alkylated product 4d or the 5,7-dialkylated product 5d.

17 We only observed the product alkylated at the C-4 position and we did not observe in the crude ^{1}H NMR any other alkylated product.

18 Cyclic ketimines such as 4-methylbenzo[*e*][1,2,3]oxathiazine 2,2-dioxide or 3-methylbenzo[*d*]isothiazole 1,1-dioxide were not reactive under the optimized reaction conditions.

19 CCDC 1875758 (3e) and CCDC 1846586 (7a) contains the supplementary crystallographic data for this paper.

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